Q3

subject, coating of an instrument used during a procedure upon the subject which results in blood vessel injury, or contacting blood of the subject during extracorporeal circulation.--

--13.(Amended) The method of claim 3, wherein the inhibitor is administered to the subject at a rate from about 2 μg/kg/hr to about 100 μg/kg/hr.--

Q4

--14.(Amended) The method of claim 3, wherein the inhibitor is coated onto a stent used during an angioplasty of the subject.--

REMARKS

Claims 1-24 were pending in the subject application. Applicants have hereinabove canceled claims 1-2, 7-8, 10 and 15-24 without prejudice or disclaimer to applicants right to pursue the subject matter of these claims in a later-filed application and amended claims 4-5, 9, 11 and 13-14. Support for these amendments may be found inter alia in the specification as follows: Claim 4: page 5, line 27; Claim 5: page 5, lines 29-31; Claim 9: page 19, lines 27-30 and page 18, Seq. I.D. No.: 5; Claim 11: page 6, lines 13-20; Claim 13: page 6, lines 26-28; Claim 14: page 6, lines 30-32. Claims 4-5, 9, 11 and 13-14 do not involve any issue of new matter. Therefore, entry of this amendment is respectfully requested such that claims 1-6, 8-9 and 11-16 will be pending.

DETAILED ACTION

Election/Restriction:

The Examiner stated that claims 7,10 and 17-24 are withdrawn from further consideration pursuant to 37 CFR 1.142 (b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. The Examiner stated that applicants timely traversed the restriction (election) requirement in Paper No. 7. The Examiner stated that applicant's election with traverse of group I, claims 1-6,8,9 and 11-16, in Paper No.7 is acknowledged. The Examiner alleged that the applicant's traversal is on the grounds that group I is not independent from groups II-VIII because they are all drawn to a method for inhibiting new tissue growth in blood vessels, of inhibiting neointimal formation in blood vessels, or preventing exaggerated restenosis in a diabetic subject, and no serious burden in required to search all these groups. The Examiner stated this is not found persuasive because of the reasons or record. The Examiner alleged that these groups are drawn to methods of using different materials having different chemical structures, different physical properties, and different biological functions: polypeptides, organic or inorganic molecules, nucleic acids and antibodies, which have different classifications. The Examiner alleged that these groups are drawn to methods that differ at least in method steps, reagents and/or dosages used, schedules used, response variables, and criteria for success. The Examiner alleged that a method of inhibiting new tissue growth or neointimal formation or preventing exaggerated restenosis in a subject is different from a method for determining whether a compound inhibits

new tissue growth in a blood vessel in a subject, and they differ at least in their objectives, method steps, reagents and/or dosages used, schedules, response variables, and criteria for success. The Examiner stated that the requirement is still deemed proper and is therefore made FINAL. The Examiner stated that claims 1-24 are pending and claims 1-6, 8, 9 and 11-16 are under consideration.

Sequence disclosures:

The Examiner alleged that this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequence set forth in 37 C.F.R. §1.82 (a)(1)(2). The Examiner alleged however, that this application fails to comply with the requirements of 37 C.F.R. §1.821 through §1.825 for the reason(s) set forth on the attached Notice To Comply with Requirements For Patent Applications Containing Nuceotide Sequence And/Or Amino Acid Sequence Disclosures.

Rejection under 35 U.S.C. §112, first paragraph:

Claims 1-6, 8-9 and 11-16:

The Examiner rejected claims 1-6, 8-9 and 11-16 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner alleged that the claims read on administering a polypeptide inhibitor of receptor for advanced glycation endproduct (RAGE) to a subject so as to inhibit new

tissue growth or neointimal formation in blood vessels or prevent exaggerated restenosis in a diabetic subject. The Examiner alleged that claim 6 specifies the inhibitor is a molecule having molecular weight of about 500 daltons to about 100 kilodaltons. The Examiner alleged that the specification only discloses using soluble RAGE, which is a truncated RAGE lacking a transmembrane domain, for the claimed method. The Examiner alleged that the claims encompass a genus of structural variants of soluble RAGE and include various unknown and unidentified polypeptide that may have the same function as soluble RAGE, i.e. inhibitor of RAGE. The Examiner alleged that the genus is highly variant because a significant number of structural differences between genus members is permitted. The Examiner alleged that the various polypeptide inhibitors of RAGE could be totally different from each other and have different structural features. The Examiner alleged that a molecule having molecular weight of about 500 daltons to about 100 kilodaltons encompasses numerous unknown and unidentified polypeptides having unknown biological functions and unknown structures. The Examiner alleged that structural features that could distinguish compounds in the genus from others in the polypeptide class are missing from the disclosure. The Examiner alleged that no common structural attributes identify the members of the genus. The Examiner alleged that the general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. The Examiner alleged that since the disclosure fails to describe common attributes or characteristics that identify members of the genus,

and because the genus is highly variant, the disclosure of soluble RAGE is insufficient to describe the genus. The Examiner alleged that this limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of numerous polypeptide inhibitors of RAGE for the claimed method in the prevent invention. The Examiner alleged the written description requirement is not satisfied for the genus.

Further, the Examiner rejected claims 1-6, 8-9 and 11-16 under 35 U.S.C. §112, first paragraph, because the specification, while being enabled for reduction of smooth muscle proliferation and migration in cartoid artery by treating Fatty Zucker rat with soluble RAGE (sRAGE) via intraperitioneal injection, allegedly does not reasonably provide enablement for any method for inhibiting new tissue growth or neointimal formation in blood vessels in a subject or preventing exaggerated restenosis in a diabetic subject by administering to said subject any polypeptide inhibitor of RAGE in vivo. The Examiner alleged that the specification does not enable any person skilled in the art to which it pertains, or with which it is mostly nearly connected, to make connected, to make and/or use the invention commensurate in scope with these claims.

The Examiner alleged that the claims are directed to a method for inhibiting new tissue growth or neointimal formation in blood vessels in a subject or preventing exaggerated restenosis in a diabetic subject by administering to said subject, such as a non-human animal, a human, or a transgenic non-human animal, a

polypeptide inhibitor of RAGE, such as sRAGE, in vivo. The Examiner alleged that claim 6 specifies the inhibitor is a molecule having molecular weight of about 500 daltons to about 100 kilodaltons. The Examiner alleged that claims 11,12,14 and 16 specify the administration route of the inhibitor, such as bolus injection, oral administration, i.v., i.p., adenovirus infection etc., or via device, such as a stent or angioplasty balloon. The Examiner alleged that claim 13 specifies the inhibitor is administered at a rate of about 2 μg/kg/hr to about 100 μg/kg/hr. The Examiner alleged that the specification discloses reduction of smooth muscle proliferation and migration in carotid artery by treating Fatty Zucker rat with soluble RAGE (sRAGE) via intraperitoneal injection. The Examiner alleged that the specification fails to provide adequate guidance and evidence for how to inhibit new tissue growth or neointimal formation in blood vessels in a subject or preventing exaggerated restenosis in a diabetic subject by administering to said subject, such as a non-human animal, a human, or a transgenic non-human animal, any polypeptide inhibitor of RAGE other than sRAGE in vivo. The Examiner alleged that the claims encompass numerous unknown and unidentified polypeptides having unknown biological functions and unknown structural features, and it is unclear whether these polypeptide could function as inhibitors of RAGE to inhibit new tissue growth or neointimal formation in blood vessels in a subject or preventing exaggerated restenosis in a diabetic subject in vivo. The Examiner alleged that the amino acid sequence of a protein determines its structural and functional properties, and

predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited.

The Examiner alleged that Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore,p.1-7), points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study" (e.g.p.6). The Examiner alleged that Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol.87,pp.6922-6926) teaches that "a single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and onocoprotein binding" (e.g. title). The Examiner alleged that Skolnick et al., 2000 (Trends in Biotech, Vol.18, p.34-39) states "sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins." The Examiner alleged that just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. The Examiner alleged that structural descriptors for protein functional sites are crucial for unlocking the secrets that "knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g.p.36, box 2). The Examiner

alleged that in view of the lack of detailed information regarding the structural and functional requirements of the polypeptide inhibitor of RAGE, and the unpredictability of polypeptide function from mere amino acid sequence, it would be unpredictable if any polypeptide other than sRAGE or polypeptide having a molecular weight of about 500 daltons to about 100 kilodaltons would function as inhibitor of RAGE to inhibit new tissue growth or neointimal formation in blood vessels in a subject or preventing exaggerated restenosis in a diabetic subject *in vivo*. The Examiner further alleged that claim 16 specifies administering a polypeptide inhibitor of RAGE via adenovirus infection. The Examiner alleged that the specification fails to provide adequate guidance for how to administer a polypeptide inhibitor via adenovirus infection. The Examiner alleged that it was known in the art that adenovirus is used for gene transfer, especially in gene therapy, but not for polypeptide transfer. The Examiner alleged that it is unclear how one skilled in the art would be able to transfer a polypeptide inhibitor of RAGE via adenovirus infection *in vivo*. The Examiner alleged that it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that it would require one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the specification is enabled.

Nevertheless, in order to further the prosecution, applicants have hereinabove amended claim 9 to more particularly describe the presently claimed invention. Applicants respectfully direct the Examiner to amended claim 9 which recites as follows:

"The method of claim 3, wherein the inhibitor is the V-domain of soluble receptor for advanced glycation endproduct (sRAGE)"

Therefore, applicants contend that claim 9 now recites a **specific structural and functional attribute** of an inhibitor of RAGE and no longer recites the Examiner's alleged limitation of not describing the entire genus of RAGE inhibitors. Accordingly, applicants contend that this amendment obviates the Examiner's above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. §102(b):

The Examiner rejected claims 1-4, 6, 8-9, 11 and 15-16 under 35 U.S.C. §102(b) as being anticipated by Park et al., 1998 (Nature Medicine, Vol. 4, No. 9, p.1025-1031). The Examiner alleged that the claims are directed to a method for inhibiting new tissue growth or neointimal formation in blood vessels in a subject or preventing exaggerated restenosis in a diabetic subject by administering to said subject, such as a non-human animal, a human, or a transgenic non-human animal, a polypeptide inhibitor of RAGE, such as sRAGE, in vivo. The Examiner alleged that claim 6 specifies the inhibitor is a molecule having molecular weight of about 500 daltons to about 100 kilodaltons. The Examiner alleged

that claims 11 and 16 specify the administration route of the inhibitor, such as bolus injection, oral administration, i.v., i.p., adenovirus infection etc., and that claim 15 specifies the subject is suffering from diabetes, acute thrombotic stroke, thrombosis as a result of peripheral vascular surgery etc. The Examiner alleged that Park et al. teaches advanced glycation endproduct (AGE) engage their receptor in cells of blood vessel wall and active mechanism linked to the development of vascular lesions. The Examiner alleged that Park et al. teaches soluble extracellular domain of RAGE completely suppress diabetic atherosclerosis in a glycemia-and lipid-independent manner (e.g. abstract). The Examiner alleged that Park et al. further teaches administering sRAGE, the extracellular two-thirds of the receptor, to a mouse via intraperitoneal injection at a dose of 3 μg/day, 20μg/day (e.g. p. 1026, right column). The Examiner alleged that sRAGE has about 318 amino acid residue encoded by 954 nucleotides, and therefore, sRAGE has a molecular weight between about 500 daltons to about 100 kilodaltons (50 kilodaltons MW protein=1.35 kb DNA). The Examiner thus alleged that claims 1-4,6,8,9,11, 15 and 16 are anticipated by Park et al.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the presently claimed invention is not anticipated by Park et al. Specifically, Park et al. fails to disclose each and every element of the presently claimed invention.

Initially, applicants respectfully direct the Examiner to claim 3 which recites as follows:

> A method for preventing exaggerated restenosis in a diabetic subject which comprises administering to the subject a pharmaceutically effective amount of an inhibitor of receptor for advanced glycation endproduct (RAGE) so as to prevent exaggerated restenosis in the subject.

Therefore, applicants contend that the present invention is directed to a method for preventing exageratted restenosis in a subject by administering an inhibitor of RAGE.

In contrast Park et al. recite the "suppression of accelerated diabetic atherosclerosis by the soluble receptor for advanced glycation endproducts." See page 1025, first column. Therefore, while Park et al. may at most disclose the suppression of accelerated diabetic atherosclerosis by soluble RAGE, it neither teaches not discloses the prevention of exageratted restenosis in a subject. Accordingly, applicants contend that Park et al. fails to disclose each and every element of the presently claimed invention.

Applicants contend that Park et al. fail to anticipate the presently claimed invention. Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. §102(a):

The Examiner rejected claims 1, 2, 4, 6, 8-9, 11 and 15-16 under 35 U.S.C. §102(a) as being anticipated by Taguchi et al., 2000 (Nature, Vol. 405, p. 354-360). The Examiner alleged that the claims are directed to a method for inhibiting new tissue growth or neointimal formation in blood vessels in a subject or preventing exaggerated restenosis in a diabetic subject by administering to said subject, such as a non-human, a human, or a transgenic non-human animal, a polypeptide inhibitor of RAGE, such as sRAGE, *in vivo*. The Examiner alleged that claim 6 specifies the inhibitor is a molecule having molecular weight of about 500 daltons to about 100 kilodaltons. The Examiner alleged that claims 11 and 16 specify the administration route of the inhibitor, such as bolus injection,. oral administration, i.v., i.p., adenovirus infection etc. The Examiner alleged that claim 15 specifies the subject is suffering from diabetes, acute thrombotic stroke, thrombosis as a result of peripheral vascular surgery etc. The Examiner alleged that Taguchi et al. teaches that RAGE is a multi-ligand member of the immunoglobulin superfamily of cell surface molecules and interacts with distinct molecules implicated in homeostasis, development and inflammation, and certain disease such as diabetes and Alzheimer's disease. The Examiner alleged that Taguchi et al. teaches that blocking the interaction of RAGE and its ligand amphoterin with sRAGE via intraperitoneal injection into mice decreased growth and metastasis of both implanted tumors and tumors developing spontaneously in susceptible mice (e.g.abstract, p. 355). The Examiner alleged that sRAGE has about 318 amino acid

residues encoded by 954 nucleotides, and therefore, sRAGE has a molecular weight between about 500 daltons to about 100 kilodaltons (50 kilodaltons MW protein=1.35kb DNA). The Examiner thus alleged that claims 1, 2, 4, 6, 8-9,11 and 15-16 are anticipated by Taguchi et al.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that Taguchi et al. fails to anticipate the presently claimed invention. Specifically, applicants contend that Taguchi et al. fails to disclose each and every element of the presently claimed invention.

Initially, applicants respectfully direct the Examiner to claim 3 which recites as follows:

> A method for preventing exaggerated restenosis in a diabetic subject which comprises administering to the subject a pharmaceutically effective amount of an inhibitor of receptor for advanced glycation endproduct (RAGE) so as to prevent exaggerated restenosis in the subject.

Therefore, applicants contend that the present invention is directed to a method for preventing exageratted restenosis in a subject by administering an inhibitor of RAGE.

In contrast, Taguchi et al. recites that "blockade of RAGE-amphoterin signalling suppresses tumor growth and metastases." See page 354, first column. Therefore, while Taguchi et al. may at

most disclose the blockade of RAGE-amphoterin signaling, it neither teaches not discloses a method for preventing exageratted restenosis in a subject by administering an inhibitor of RAGE.

Accordingly, applicants contend that Taguchi et al. fail to disclose each and every element of the presently claimed invention.

Applicants contend that Taguchi et al. fail to anticipate the presently claimed invention. Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. §102(b):

The Examiner rejected claims 1-4, 6, 8-9, 11 and 15-16 under 35 U.S.C. §102(b) as being anticipated by Stern et al., 1998 (WO 98/22138). The Examiner alleged that the claims are directed to a method for inhibiting new tissue growth or neointimal formation in blood vessels in a subject or preventing exaggerated restenosis in a diabetic subject by administering to said subject, such as a non-human animal, a human, or a transgenic non-human animal, a polypeptide inhibitor of RAGE, such as sRAGE, *in vivo*. The Examiner alleged that claim 6 specifies the inhibitor is a molecule having molecular weight of about 500 daltons to about 100 kilodaltons. The Examiner alleged that claims 11 and 16 specify the administration route of the inhibitor, such as bolus injection, oraladministration,i.v., i.p., adenovirus infection etc. The Examiner alleged that claim 15 specifies the subject is suffering from diabetes, acute thrombotic stroke, thrombosis as a result of

peripheral vascular surgery etc. The Examiner alleged that Stern et al. teaches a method for treating symptoms of diabetes in a diabetic subject by using agents that inhibit binding of AGE to RAGE, wherein the agent could be a polypeptide such as sRAGE and the symptoms comprise abnormal wound healing, symptom of a heart attack, symptoms of a stroke, symptoms of peripheral vascular disease, amputation, symptoms of kidney disease, or inflammation etc (e.g. p. 5, 7, 9 and 23). The Examiner alleged that Stern et al. further teach that the subject could be a human, mouse, cow, pig etc., and the administration route of the agent could be intraperitoneal, i.v., intralesional, liposome-mediated delivery, oral, nasal, topical, ocular or otic delivery, and the dose ranges from 200ng/day/kg to 200,000ng/day/kg (e.g. P. 7 and 24). The Examiner alleged that sRAGE has about 318 amino acid residues encoded by 954 nucleotides, and therefore, sRAGE has a molecular weight between about 500 daltons to about 100 kilodaltons (50 kilodaltons MW protein=1.35kb DNA). The Examiner thus alleged that claims 1-4, 6, 8, 9, 11 and 15-16 are anticipated by Stern et al.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the Stern et al. does not anticipate the claims of the present invention. Specifically, applicants contend that Stern et al. fails to disclose each and every element of the presently claimed invention.

Initially, applicants respectfully direct the Examiner to claim 3 which recites as follows:

> A method for preventing exaggerated restenosis in a subject which comprises administering to the subject a pharmaceutically effective amount of an inhibitor of receptor for advanced glycation endproduct (RAGE) so as to prevent exaggerated restenosis in the subject.

Therefore, applicants contend that the present invention is directed to a method for preventing exageratted restenosis in a subject by administering an inhibitor of RAGE.

In contrast, Stern et al. recites that "the present invention provides a method for treating symptoms of diabetes in a diabetic subject which comprises administering to the subject a therapeutic amount of an agent which inhibits binding of advanced glycation endproducts to any receptor for advanced glycation endproducts so as to treat symptoms of diabetes in the subject." See page 3, summary of the invention. Therefore, while Stern et al. may at most disclose a method for treating symptoms of diabetes in a diabetic subject, it neither teaches not discloses a method for preventing exageratted restenosis in a subject by administering an inhibitor of RAGE.

Accordingly, applicants contend that Stern et al. fails to disclose each and every element of the presently claimed invention. Applicants contend that Stern et al. fail to anticipate the presently claimed invention. Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. §103:

The Examiner alleged that this application currently names joint inventors. The Examiner States in considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. The Examiner stated that applicant is advised of the obligation under 37 C.F.R. §1.56 to point out the inventor and invention dated of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §102(f) or (g) prior art under 35 U.S.C. §103(a).

The Examiner rejected claims 1-3, 12 and 13 under 35 U.S.C. §103(a) as being unpatentable over Stern et al., 1998 (W0 98/22138) in view of Nabel et al., 1997 (US Patent No. 5,698,531). The Examiner alleged that the claims are directed to a method for inhibiting new tissue growth or neointimal formation in blood vessels in a subject or preventing exaggerated restenosis in a diabetic subject by administering to said subject, such as a non-human animal, a human, or a transgenic non-human animal, a polypeptide inhibitor of RAGE, in vivo. The Examiner alleged that claim 12 specifies the device to be placed within the subject is a sent of an angioplasty balloon. The Examiner alleged that claim 13 specifies the inhibitor is administered at a rate from about 2 μg/kg/hr to about 100 μg/kg/hr. The Examiner alleged that Stern et al. teaches a method for treating symptoms of diabetes in a diabetic subject by

using agent that inhibits binding of AGE to RAGE, wherein the agent could be polypeptide such as sRAGE and the symptoms comprise abnormal wound healing, symptom of heart attack, symptoms of a stroke, symptoms of peripheral vascular disease, amputation, symptoms of kidney disease, or inflammation etc(e.g. p. 5, 7, 9 and 23). The Examiner alleged that Stern et al. further teaches that the subject could be a human, mouse, cow, pig etc., and the administration route of the agent could be intraperitoneal, i.v., intralesional, liposome-mediated delivery, oral, nasal, topical, ocular or otic delivery, and the dose ranges from 200 ng/day/kg to 200,000 ng/day/kg (e.g. p. 7 and 24). The Examiner stated that Stern et al. does not teach using a stent or angioplasty balloon to deliver inhibitor or that the inhibitor is administered at a rate from about 2 μg/kg/hr to about 100 μg/kg/hr.

The Examiner alleged that Nabel et al. teaches a method of delivering proteins to the walls of the blood vessel or in the tissue perfused by the vessel, in a patient, via a balloon catheter for treating diseases in vivo (e.g. abstract). The Examiner alleged that it would have been obvious for one of ordinary skill at the time of the invention to use a balloon catheter as taught by Nabel et al. to deliver the polypeptide inhibitor of RAGE, such as sRAGE, as taught by Stern et al. for the claimed method because both the protein taught by Nabel and the Polypeptide inhibitor taught by Stern are both polypeptides, and Nabel teaches using balloon catheter to deliver a protein for treating a disease. The Examiner alleged that it would be obvious for one of ordinary skill

to substitute one polypeptide with another polypeptide on a balloon catheter. The Examiner alleged that it also would have been obvious for one of ordinary skill at the time of the invention to administer sRAGE at a rate from about 2μg/kg/hr to about 100 μg/kg/hr because Stern et al. teaches using a dose ranges from 200 ng/day/kg to 200,000 ng/day/kg and determining effective dose is routine optimization of a result-effective variable and is obvious to a person of ordinary skill in the art. The Examiner alleged that one having ordinary skill at the time the invention was made would have been motivated to administer an inhibitor of RAGE via balloon catheter to a patient according to the collective teachings of Stern et al. and Nabel et al. in order to treat symptoms of diabetes in a diabetic subject, wherein the symptoms comprise wound healing, symptom of heart attack, symptoms of a stroke, symptoms of peripheral vascular disease, amputation, symptoms of kidney disease, or inflammation etc., as taught by Stern with reasonable expectation of success.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants respectfully contend that the Examiner has misapprehended the presently claimed invention and that the cited references, namely Stern et al. in view of Nabel et al., do not render obvious the claimed invention.

Initially, applicants respectfully direct the Examiner to claim 3 which recites as follows:

> A method for preventing exaggerated restenosis in a subject which comprises administering to the subject a pharmaceutically effective amount of an inhibitor of receptor for advanced glycation endproduct (RAGE) so as to prevent exaggerated restenosis in the subject.

Therefore, applicants contend that the present invention is directed to a method for preventing exaggerated restenosis in a subject by administering an inhibitor of RAGE.

Stern et al. does not teach any use of an inhibitor of RAGE to treat exaggerated restenosis in a subject. Furthermore, the Examiner recites that Stern et al. "does not teach using a stent or angioplasty balloon to deliver inhibitor." See page 13, paper No. 8. Therefore, there is no motivation in Stern et al. to use an inhibitor of RAGE for the claimed purpose, i.e. preventing exaggerated restenosis in a subject by administering an inhibitor of RAGE.

To compensate for the lack of any disclosure of the presently claimed invention in Stern et al., i.e. preventing exaggerated restenosis in a subject by administering an inhibitor of RAGE, the Examiner relies on Nable et al. to "support the use of the polypeptide of Stern for the claimed method because both the protein taught by Nabel and the polypeptide inhibitor taught by Stern are both polypeptides and Nabel teaches using balloon catheter to deliver a protein for treating disease." See page 13, paper No. 8. Further, the Examiner recited that "Nabel teaches a

method of delivering proteins to the walls of the blood vessel" See page 13, paper No. 8. However, applicants respectfully point out that the Examiner has misapprehended the applicants presently claimed invention. The presently claimed invention is a method for preventing exagerated restenosis in a subject by administering an inhibitor of RAGE, not a method for delivering proteins to the walls of a blood vessel. Applicants contend that Nable et al. does not offer what Stern et al. fails to disclose, i.e. a method for preventing exaggerated restenosis in a subject by administering an inhibitor of RAGE.

The applicants contend that the cited references, namely Stern et al. in view of Nabel et al. do not teach or suggest a method for preventing exagerated restenosis in a subject by administering an inhibitor of RAGE and do not render obvious the presently claimed invention. Accordingly, applicants contend that these comments obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. §103(a):

The Examiner rejected claims 1-3, 5, 11-12 and 14 under 35 U.S.C. §103(a) as being unpatentable over Stern et al., 1998 (WO 98/22138 in view of Donovan et al., 1998 (US Patent No.5,833,651). The Examiner alleged that the claims are directed to a method for inhibiting new tissue growth or neointimal formation in blood vessels in a subject or preventing exaggerated restenosis in a diabetic subject by administering to said subject, such as a non-

human animal, a human, or a transgenic non-human animal, a polypeptide inhibitor of RAGE, such as sRAGE, *in vivo*. The Examiner alleged that claim 5 specifies the subject has undergone an angioplasty procedure or surgery to implant a stent in a blood vessel. The Examiner alleged that claim 12 specifies the device to be placed within the subject is a stent of an angioplasty balloon. The Examiner alleged that claim 14 specifies that the inhibitor is coated onto a stent used during an angioplasty of the patient. The Examiner alleged that Stern et al. teaches a method for treating symptoms of diabetes in a diabetic subject by using agent that inhibits binding of AGE to RAGE, wherein the agent could be polypeptide such as sRAGE and the symptoms comprise abnormal wound healing, symptom of a heart attack, symptoms of a stroke, symptoms of peripheral vascular disease, amputation, symptoms of kidney disease, or inflammation etc (e.g. p. 5, 7, 9 and 23). The Examiner alleged that Stern et al. further teaches that the subject could be a human, mouse, cow, pig etc., and the administration route of the agent could be intraperitoneal, i.v., intralesional, liposome-mediated delivery, oral, nasal, topical, ocular or otic delivery, and the dose ranges from 200ng/day/kg to 200,000 ng/day/kg (e.g. p.7 and 24). The Examiner stated that Stern et al. does not teach a stent or angioplasty balloon to deliver inhibitor.

The Examiner alleged that Donovan teaches using a stent to deliver therapeutic substances, such as viruses, nucleic acids, drugs and therapeutic proteins to a lumen wall of the body for treating or preventing disease (e.g. column 1,2). The Examiner alleged that it

would have been obvious for one of ordinary skill at the time of the invention to use a stent as taught by Donovan et al. to deliver the polypeptide inhibitor of RAGE, such as sRAGE, as taught by Stern et al. for the claimed method because both the therapeutic protein taught by Donovan et al. and the polypeptide inhibitor taught by Stern et al. are both polypeptide and Donovan et al. teaches using a stent to deliver a protein for treating a disease. The Examiner alleged that it would be obvious for one if ordinary skill to substitute one polypeptide with another polypeptide on a stent. The Examiner alleged that one having ordinary skill in the art at the time the invention was made would have been motivated to administer an inhibitor of RAGE via stent, e.g. stent coated with said inhibitor, to a patient according to the collective teachings of Stern et al. and Donovan et al., in order to treat symptom of a heart attack, symptoms of a stroke, symptoms of peripheral vascular disease, amputation, symptoms of kidney disease, or inflammation etc., as taught by Stern et al. with reasonable expectation of success.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants respectfully contend that the Examiner has misapprehended the presently claimed invention and that the cited references, namely Stern et al. in view of Nabel et al., do not render obvious the claimed invention.

Initially, applicants respectfully direct the Examiner to claim 3 which recites as follows:

> A method for preventing exaggerated restenosis in a subject which comprises administering to the subject a pharmaceutically effective amount of an inhibitor of receptor for advanced glycation endproduct (RAGE) so as to prevent exaggerated restenosis in the subject.

Therefore, applicants contend that the present invention is directed to a method for preventing exaggerated restenosis in a subject by administering an inhibitor of RAGE.

Stern et al. does not teach any use of an inhibitor of RAGE to treat exaggerated restenosis in a subject. Furthermore, the Examiner recites that Stern et al. "does not teach using a stent or angioplasty balloon to deliver inhibitor." See page 13, paper No. 8. Therefore, there is no motivation in Stern et al. to use an inhibitor of RAGE for the claimed purpose, i.e. preventing exaggerated restenosis in a subject by administering an inhibitor of RAGE.

To compensate for the lack of any disclosure of the presently claimed invention in Stern et al., i.e. preventing exaggerated restenosis in a subject by administering an inhibitor of RAGE, the Examiner relies on Donovan et al. to provide what is missing from Stern et al. However, applicants respectfully point out that the Examiner has misapprehended the applicants presently claimed invention. The presently claimed invention is a method for preventing exagerated restenosis in a subject by administering an inhibitor of RAGE, not a method for delivering proteins to the

walls of a blood vessel. Applicants contend that Donovan et al. does not offer what Stern et al. fails to disclose, i.e. a method for preventing exaggerated restenosis in a subject by administering an inhibitor of RAGE.

The applicants contend that the cited references, namely Stern et al. in view of Donovan et al. do not teach or suggest a method for preventing exagerated restenosis in a subject by administering an inhibitor of RAGE and do not render obvious the presently claimed invention. Accordingly, applicants contend that these comments obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Summary

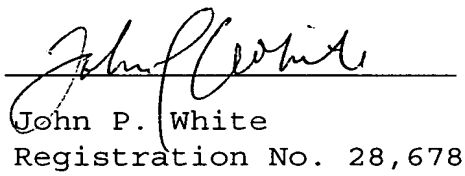
For the reasons set forth hereinabove, applicants respectfully quest that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims, i.e. claims 3-5, 9, 11 and 13-14.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $460.00 for a three-month extension of time is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required,

authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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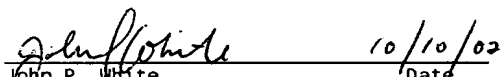
I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.



10/10/02
John P. White Date
Reg. No. 28,678